PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

van Oosterhout et al.

Serial No.: 09/578,361

Filed: May 24, 2000

For: METHODS AND MEANS FOR THE TREATMENT OF IMMUNE RELATED DISEASES

Examiner: Ron Schwadron, Ph.D.

Group Art Unit: 1644

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BRIEF ON APPEAL

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Commissioner for Patents
P.O. Box 1450
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Sirs:

This brief is submitted in TRIPLICATE pursuant to 37 C.F.R.§ 1.192(a) and in the format required by 37 C.F.R. § 1.192(c):

(1) REAL PARTY IN INTEREST

The real party in interest in the present pending appeal is Immunotoko BV, assignee of the pending application as recorded with the United States Patent and Trademark Office on April 2, 2001, at Reel 011662, Frame 0788.

(2) RELATED APPEALS AND INTERFERENCES

Neither the Appellants, the Appellants' representative, nor the Assignee is aware of any pending appeal or interference which would directly affect, be directly affected by, or have any bearing on the Board's decision in the present pending appeal.

(3) STATUS OF THE CLAIMS

Claims 1-8, 10-13, 15 and 18-26 stand rejected.

No claims are allowed.

The rejections of claims 1-8, 10-13, 15 and 18-26 are being appealed.

(4) STATUS OF AMENDMENTS

An amendment under 37 C.F.R. § 1.116 was filed on December 5, 2002. An Advisory Action mailed February 5, 2003 notified Appellants that the amendment had not overcome the Examiner's rejections and would not be entered.

(5) SUMMARY OF THE INVENTION

The claimed invention provides means and methods for treating unwanted side effects in transplantations, such as graft versus host disease and allograft rejection, through the elimination of T-cells and NK-cells. The invention provides immunotoxins having an antibody and a toxic substance, wherein "cocktails" of the conjugates are directed to different targets associated with a population of cells in the T-cell or NK-cell lineage, wherein one target is chosen from CD3 or CD7. The preferred combination is a cocktail directed against both.

(6) ISSUES

A. Whether claims 1-8, 10-13, 15, and 18-26 are unpatentable less than 35 U.S.C. § 102(a) as anticipated by van Oosterhout, Y.V.J.M. et al., *Suitability of a Cocktail of CD34and CD7 Ricin A-Immunotixins for in vivo Treatment of Acute Graft-Versus-Host Disease*, Thirty-Ninth Annual Meeting of the American Society of Hematology, San Diego, California, USA, December 5-9, 1997; BLOOD 90 (10 Suppl. 1 part 2), November 15, 1997, 376B; ISSN: 0006-4971, page 376B, column two, paragraph 4439 (hereinafter "van Oosterhout").

B. Whether claims 1-5, 7-13, 15, 18, 19, and 21-26 are unpatentable under 35 U.S.C. § 102(b) as being anticipated by WO 89/06967 to Scannon et al.(hereinafter "Scannon").

C. Whether claims 1-8, 10-13, 15, and 18-26 are unpatentable under 35 U.S.C. § 103(a) as being unpatentable over Scannon in view U.S. Patent 6,261,535 to Thorpe et al. (hereinafter "Thorpe").

(7) GROUPING OF CLAIMS

The grouping of the claims is as follows:

Group I: Claims 1, 3-8, 10-13, 18, 23 and 26

Claims 1, 3-8, 10-13, 18, 23 and 26 do not stand or fall together with the other claims of Group II, Group III, or Group IV. Claims 1, 3-8, 10-13, 18, 23 and 26 do not fall with the other claims, as it is asserted that claims 1, 3-8, 10-13, 18, 23 and 26 are separately patentable from the other claims and from each other.

Group II: Claims 2, 15, 19-22

Claims 2, 15, and 19-22 do not stand together with the other claims of Group I, Group III, or Group IV. Claims 2, 15, and 19-22 do not fall with the other claims, as it is asserted that claims 2, 15, and 19-22 are separately patentable from the other claims and from each other.

Group III: Claim 24

Claim 24 does not stand together with the other claims of Group I, Group II, or Group IV. Claim 24 does not fall with the other claims, as it is asserted that claim 24 is separately patentable from the other claims.

Group IV: Claim 25

Claim 25 does not stand together with the other claims of Group I, Group II, or Group III. Claim 25 does not fall with the other claims, as it is asserted that claim 25 is separately patentable from the other claims.

(8) ARGUMENT

(i) 35 U.S.C. § 112, first paragraph

There are no rejections or issues under 35 U.S.C. 112, first paragraph.

(ii) 35 U.S.C. § 112, second paragraph

There are no rejections or issues under 35 U.S.C. 112, second paragraph.

(iii) 35 U.S.C. § 102(a)

Claims 1-8, 10-13, 15, and 18-26 stand rejected under 35 U.S.C. § 102(a) as being anticipated by van Oosterhout (*See,* Final Office Action, mailed October 18, 2002, at page 1).

In the Office Action mailed December 11, 2001, the Examiner, at page 1, requested that appellants "supply the date that the instant reference was published in order to determine if the instant rejections should be made under 35 U.S.C. § 102 (b) or (a)."

The Examiner provided, in the Notice of References Cited, a van Oosterhout publication with a known publication date of 1997, but no day or month for the publication. The publication date the Examiner requested was provided by Appellants in the communication submitted on June 11, 2002 with the publication date of the reference in question being November 15, 1997. As the instant application claims a priority date of March 23, 1998 from U.S. Provisional Application 60/079,086, the 1997 van Oosterhout publication was not more than one year prior from the effective filing date of the instant application and 35 U.S.C. 102(b) does not apply (*See,* M.P.E.P. § 706.02). Because the cited reference was not more than one year before the effective filing date, the rejection for anticipation by the cited reference would have to fall under 35 U.S.C. § 102(a) (*See*, M.P.E.P. § 706.02(a) "For 35 U.S.C. 102(a) to apply, the reference must have a publication date earlier in time than the effective filing date of the application, and must not be the applicant's own work").

The M.P.E.P. § 706.02(b) provides that "[a] rejection based on 35 U.S.C. § 102(a) can be overcome by: . . . (D) Filing an affidavit or declaration under 37 C.F.R. 1.132 showing that the reference invention is not by 'another.'" M.P.E.P., 700-25 (Feb. 2003). As any anticipation rejection over the 1997 van Oosterhout *et al.* reference would have to fall under 35 U.S.C. § 102(a), Appellants filed the requisite 37 C.F.R. 1.132 declarations on June 11, 2002 to overcome the rejection as being the "applicant's own work." In the Final Office Action, the examiner rejected the declarations as not being compliant with M.P.E.P. § 715.05.

To correct the shortcomings of the previously submitted declarations, Appellants submitted replacement declarations complying with § 715.05. The Patent Office received these declarations on December 9, 2002. The advisory action mailed by the Examiner on February 5, 2003, however, was silent as to the sufficiency of the replacement declarations in overcoming the 35 U.S.C. § 102(a) based rejection. On March 5, 2003, Applicants inquired into the effect of the replacement declarations, but no reply has been forthcoming. Therefore, the current status of the rejection, in light of the substitute declarations, is unknown. As the replacement declarations are believed to comply with the requirements for 37 C.F.R. 1.132 declarations, Appellants respectfully submit that the rejection has been overcome and request that claims 1-8, 10-13, 15 and 18-26 be allowed (*see*, *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982); M.P.E.P. § 2131.01).

(iv) 35 U.S.C. § 102(b)

Claims 1-5, 7-13, 15, 18, 19 and 21-26 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Scannon (*See,* Final Office Action, at page 1). As the claims of Group I stand with independent claim 1, and the claims of Group II stand with independent claim 15, and Groups III and IV contain only single independent claim each (claims 24 and 25 respectively), only claims 1, 15, 24, and 25 will be addressed.

In asserting that Scannon anticipates claims 1-5, 7-13, 15, 18, 19 and 21-26, the Examiner refers to page 4, lines 1-12 in Scannon, which states: "the delivery component of the immunosupressive immunotoxin may *comprise* one pan T-cell reactive immunoglobulin or a collection of immunoglobulins reactive with a plurality of T-cell markers, such as those associated

with antigen clusters CD2, CD3, CD4, CD5, CD6, CD7, CD9, CD11, and CD45R" (emphasis added).

As amended, independent claim 1 recites "a pharmaceutical composition for eliminating or reducing the number of unwanted CD3 and/or CD7 positive cells, said pharmaceutical composition *consisting essentially of*: first molecules directed against CD3, and second molecules, distinct from said first molecules, said second molecules directed against CD7, wherein at least one of said first and said second molecules include a toxic moiety."

As amended, independent claim 15 recites "a method of treating a disease state in a subject believed to be suffering therefrom, said disease state comprising at least one of Graft vs. Host disease, graft rejections, T-cell leukemias, T-cell lymphomas, other lymphomas, other CD3 and/or CD7 malignancies, autoimmune diseases, and infectious immune disease, said method comprising administering to the subject an amount of a pharmaceutical composition *consisting essentially of*: first molecules directed against a CD3 positive cell, and second molecules, distinct from said first molecules, directed against a CD7 positive cell, wherein at least the second molecules include a toxic moiety."

Independent claim 24 recites "a pharmaceutical composition for eliminating or reducing the number of unwanted CD3 and/or CD7 positive cells, said pharmaceutical composition *consisting essentially of*: anti-CD3 antibodies; and anti-CD7 antibodies, wherein each of said anti-CD3 antibodies and said anti-CD7 antibodies include a toxic moiety."

Independent claim 25 recites "a method of treating a disease state in a subject believed to be suffering therefrom, said disease state comprising at least one of Graft vs. Host disease, graft rejections, T-cell leukemias, T-cell lymphomas, other lymphomas, other CD3 and/or CD7 malignancies, autoimmune diseases, and infectious immune diseases, said method comprising administering to the subject an amount of a pharmaceutical composition *consisting essentially of*: anti-CD3 antibodies; and anti-CD7 antibodies, wherein each of said anti-CD3 antibodies and said anti-CD7 antibodies include a toxic moiety."

The Transitional Phrase "Consisting Essentially Of"

Anticipation requires that the same invention, including each element of the claims be known or used by others before it was invented by the patentee. *Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302, 36 USPQ 1101, 1103 (Fed. Cir. 1995)(emphasis added). In claims 1, 15, 24, and 25 the transitional phrase "'consisting essentially of' [explicitly directs] the claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention." M.P.E.P. § 2111.03, *citing In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976)(emphasis in original omitted). See, also, *AFG Indus. v. Cardinal IG Co.*, 239 F.3d 1239, 57 USPQ 1776 (Fed. Cir. 2001). As such, claims 1, 15, 24, and 25 include pharmaceutical compositions or methods targeting only CD3 and CD7. This claimed invention does not exist as part of the Scannon disclosure, where one is free to use any, all, or none of the disclosed antigens. For this reason, under *Hoover*, claims 1, 15, 24, and 25 are not anticipated by Scannon and are patentable thereover.

In response to Appellants' position, the Examiner argues M.P.E.P. § 2111.03, which states that "[f]or the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the Specification or claims of what the basic and novel characteristics actually are, 'consisting essentially of' will be construed as equivalent to 'comprising.'" In citing this section, the Examiner argues that Appellants have made no clear indication in the Specification of what the basic and novel characteristics of the claimed invention are, and therefore the phrase "consisting essentially of" in claims 1, 15, 24, and 25 should be construed as equivalent to "comprising" (*See,* Final Office Action, at page 2; Advisory Action, mailed February 5, 2003, at continuation sheet).

Construing the language "consisting essentially of" in claims 1, 15, 24, and 25 as equivalent to "comprising" destroys the intended interpretation of Appellants' claims. Ignoring the transitional phrase chosen by Appellants, claims 1, 15, 24, and 25 would arguably be anticipated by Scannon. However, Appellants respectfully submit that a clear indication does exist in the Specification of what the basic and novel characteristics of the invention are, and therefore the transitional phrase "consisting essentially of" in claims 1, 15, 24, and 25 is being misinterpreted as "comprising." Under *Hoover*, the transitional phrase "consisting essentially of" precludes anticipation of these claims by Scannon.

The Specification at page 4 specifically recites that the claimed invention "provides a pharmaceutical composition for eliminating or reducing the number of unwanted CD3 and/or CD7 positive cells" and that "[t]ypically these cells are T-cells or NK-cells or other cells playing a role in GVHD or allograft rejection." These statements provide the basic novel characteristics of the claimed invention, namely, the treatment of immune related disease through the elimination of cells in the T-cell and NK-cell lineages. Every aspect of the Specification is focused on this basic goal. Additionally, when the Specification, at page 6, provides for an expansion of target molecules beyond CD3 and CD7, these suggested molecules remain specific to the T-cell or NK-cell lineage. This is in contrast to the laundry list provide by Scannon at page 4 which also lists CD9 and CD11. CD9 and CD11 target cells outside the T-cell or NK-cell lineage, namely cells of the myeloid lineage including eosinophils, basophils, platelets. *See, e.g.,* C. Stain et al., *Human blood basophils display a unique phenotype including activation linked membrane structures*, 70(6) Blood 1872-9 (1987); Research Diagnostics Inc., *Anti-Human CD Clustered (CD) Antibodies* <http://www.researchd.com/reicdabs/cdindex.htm> (last updated May 28, 2001). Thus, Appellants submit that the basic characteristics of the invention are well defined in the Specification, and where the Specification discusses changes in the invention, it limits the discussion to materials that would not materially alter the basic goal of affecting cells in the T-cell and NK-cell lineages.

The claimed invention is novel over Scannon due to the claimed precise targeting of cells in the T-cell and NK-cell lineages. Scannon, as outlined *supra*, suggests targeting the entire myeloid lineage in addition to T-cells and NK-cells, while the claimed invention is directed to cells in the T-cell and NK-cell lineages. The claimed invention is further inventive as Scannon teaches away from the claimed invention. Scannon recites on page 9 that "[i]deally, the immunoglobulins will only minimally, if at all, cross-react with other leukocyte subsets [other than T-cells]." The claimed invention, however, is specifically designed to react with NK-cells, another subset of leukocytes (see, Specification at pages 9 and 10). As such, the specific targeting of NK-cells through CD7 is novel over Scannon.

The M.P.E.P. § 2111.03 further directs that "[i]f an applicant contends that additional steps or materials in the prior art are excluded by the recitation of 'consisting essentially of,' applicant has the burden of showing that the introduction of additional steps or components would materially

change the characteristics of the applicant's invention." Clearly, the additional materials in Scannon, namely CD9 and CD11, are excluded by the recitation of "consisting essentially of" in claims 1, 15, 24, and 25. The addition of CD9 or CD11 to the claimed invention would materially alter the basic goal of only targeting T-cells and NK-cells by further targeting cells in the myeloid lineage.

As the entire Specification is directed to the destruction of T-cells and NK-cells, it is clear that targeting cells outside of the T-cell and NK-cell lineages, as taught by Scannon, would result in a material alteration of the novel and basic characteristics of the claimed invention. Therefore, Appellants respectfully submit that the language "consisting essentially of" in claims 1, 15, 24, and 25 must be read properly in accordance with M.P.E.P. § 2111.03 and that claims 1, 15, 24, and 25 are therefore, under *Hoover*, not anticipated by Scannon. Furthermore, as all other claims depend, either directly or indirectly, from independent claims 1, 15, 24, and 25, Appellants respectfully request that the 35 U.S.C. § 102(b) rejection be withdrawn and the claims allowed.

Immunotoxins Comprising CD3 and CD7 are not Enabled by Scannon

"In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or anticipated' within section 102, the stated test is whether a reference contains an enabling disclosure . . . ." *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968). Scannon does not provide an enabling disclosure such that one skilled in the art at the time the invention was made could employ molecules directed at either CD3 or CD7 to eliminate or reduce the number of CD3 or CD7 positive cells without undue experimentation.

A subpart of the test for enablement, as provided in M.P.E.P. § 2164.03, is the relationship between predictability in the art and the embodiments disclosed in the anticipating reference. Specifically:

> A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. However, in an application directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. This is because it is not obvious from the disclosure of one species what other species will work (citations omitted).

Scannon reduces to practice but a single embodiment: the creation and testing of an immunotoxin targeting the CD5 molecule. This contrasts with the 11 different target molecules that are identified in the Specification, a mere two of which, CD3 and CD7, are cited by the examiner as anticipating the present claims.[1] As such, it would be unusual for the single embodiment of CD5 disclosed in Scannon to provide an adequate basis to support the generic use of 10 other target molecules or the extensive number of possible combinations thereof.[2,3]

Furthermore, the efficacy of targeting the CD3 and CD7 markers to destroy T-cells relies heavily on the physiologic activity of the cells positive for CD3 and CD7; the specificity and complexity of the large number of diverse molecules that can be used to target CD3 and CD7; how highly the target molecules are expressed on the target cell population; and the response of the CD3 and CD7 positive cells will have to the binding of any targeting molecule used. Therefore, whether CD3 or CD7 were adequate targets for the destruction of T-cells or NK-cells was unpredictable by one skilled in the art without further and substantial experimentation. Scannon was, at best, merely an invitation to those skilled in the art to experiment using the list of possibilities provided (*See, In re O'Farrell*, 853 F.2d 984, 7 USPQ2d 1673 (Fed. Cir. 1988)). Thus, Appellants respectfully submit that the targeting of T-cells and NK-cells through the use of CD3 and CD7 is not enabled by the disclosure in Scannon and that therefore claims 1, 15, 24, and 25 are not anticipated by Scannon. Furthermore, as all other claims depend, either directly or indirectly from independent claims 1, 15, 24, and 25, Appellants respectfully request that the 35 U.S.C. § 102(b) rejection be withdrawn and the claims allowed.

(iv) 35 U.S.C. § 103

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[1] CD2, CD3, CD4, CD5, CD6, CD7, CD9, CD11, and CD45R are taught at page 4 line 6 of Scannon. CD8 and TAC are taught at page 9 line 18.

[2] The 11 suggested molecules taken together give rise to 2047 possible combinations.

[3] Although examined in Japan and the European Patent Office, no patent has ever issued from this 1989 PCT application of Scannon. While this is not direct evidence for a lack of enablement, it does suggest fatal flaws in the Scannon application, of which a lack of enablement seems very likely.

Claims 1-8, 10-13, 15, and 18-26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Scannon in view of Thorpe (*See*, Final Office Action, mailed October 18, 2002, at pages 2-3). As the claims of Group I stand with independent claim 1, and the claims of Group II stand with independent claim 15, and Groups III and IV contain only single independent claim each (claims 24 and 25 respectively), only claims 1, 15, 24, and 25 will be addressed.

As the Examiner notes at page 3 of the Final Office Action, the prior art in Thorpe relied on by the Examiner relates only to the use of deglycosylated ricin A. As such, the Examiner's arguments of obviousness concerning all other aspects of the claimed invention rely solely on the disclosure of Scannon. Therefore, Appellants will focus their arguments on reasons the claimed invention is not obvious in light of Scannon and thus not obvious in regards to Scannon in view of Thorpe.

The Claimed Invention Possesses Improved Properties not Present in the Prior Art

"Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness." M.P.E.P. § 716.02(a). In the claimed invention, a combination of molecules directed against CD3 and CD7 is used to eliminate T-cells and NK-cells. Although the examiner alleges that such a combination is obvious in light of Scannon, this reference does not anticipate the degree to which this combination would be successful. Scannon proposes combinations of T-cell markers to "ensure a broad spectrum of T-cell neutralization (Scannon at page 9). No where does Scannon discuss the possibility of synergistic effects through the targeting of two or more T-cell specific markers. This is in marked contrast to what is seen by the combination of targeting both CD3 and CD7 as in the claimed invention.

The Specification at pages 8 and 33 discusses the unexpected results from the targeting of both markers. In these experiments, the authors used cultures of Primary Blood Lymphocytes (PBLs) to test the efficacy of their immunotoxin combinations. Molecules directed solely against CD3 resulted in a 100-fold reduction of PBL numbers in culture. Molecules directed solely against CD7 resulted in an 87-fold reduction of PBLs numbers in culture. If an additive effect were expected, a combination of molecules directed at CD3 and CD7 would result in a 187-fold reduction

at best. Furthermore, one skilled in the art might expect an even lower number because CD3 and CD7 are co-present on certain cell types and therefore the cell types targeted would overlap to a certain extent and therefore result in a less than additive effect. Surprisingly, when a half dose of molecules directed at CD3 is combined with a half dose of molecules directed at CD7, a 1770 fold reduction in the number of PBLs results. As such, this combination results in nearly 10-fold fewer cells surviving than the number expected through an additive effect alone.

This unexpected increase in activity is highly significant as the entire invention is directed toward removing as many T-cells and NK-cells as possible so as to reduce the severity of any resulting GVHD. The Specification, at page 1, relates that even when 98% of lymphocytes are removed from a graft, GVHD can still occur. This suggests that even small numbers of untreated lymphocytes can remain problematic and that a small increase in the efficacy of removing these cells will result in a significant drop in either the occurrence or severity of any GVHD. This is borne out in the ability to treat relapses of GVHD with low doses of corticosteroids wherein the first instance the GVHD was not (*See,* Specification at pages 5 and 7). As these results are unexpected, unobvious, as well as statistically and practically significant, Appellants respectfully submit that rejections be reversed and claims 1, 15, 24, and 25 allowed. Further, as all other claims depend, either directly or indirectly from independent claims 1, 15, 24, and 25, Appellants respectfully request that the 35 U.S.C. § 103(a) rejection be completely withdrawn and all claims allowed.

One Skilled in the Art Would not be Motivated to Choose the Combination of CD3 and CD7

M.P.E.P. § 2144.08(II)(A) provides that in order "[t]o establish a *prima facie* case of obviousness in a genus-species chemical composition situation, . . ., it is essential that Office personnel find some motivation or suggestion to make the claimed invention in light of the prior art teachings." The Examiner, at page 3 of the Final Office Action, alleges that Scannon teaches the use of a pharmaceutical composition containing antiCD3 and antiCD7 to treat GVHD. However, Scannon never explicitly teaches the claimed CD3/CD7 combination. At page 3, Scannon provides a laundry list of antibodies directed to CD3 **or** CD7 as possibilities for "an immunotoxin comprising **an** anti-pan T-cell monoclonal antibody" (emphasis added). This language suggests that either CD3 or CD7 may be used, but not both together

At page 4, Scannon teaches that an "immunosupressive immunotoxin may comprise one pan T-cell reactive immunoglobulin or a collection of immunoglobulins reactive with a plurality of T-cell markers, such as those associated with antigen clusters CD2, CD3, CD4, CD5, CD6, CD7, CD9, CD11, and CD45R." This teaching provides a genus consisting of all T-cell markers, of which the combination of clusters CD3 and CD7 are but a single species. Thus, in order to establish a *prima facie* case of obviousness, the Examiner must find some motivation or suggestion in the prior art to make the claimed invention, including what motivation there was in the prior art to make the claimed invention. The Examiner provides no indication of what the motivation in the prior art for a combination of CD3 and CD7 other than its membership in the large genus provided by Scannon at page 4 (*See,* Final Office Action page 3). On this basis Appellants respectfully submit that the Examiner has not established a *prima facie* case of obviousness, and therefore request that the 35 U.S.C. § 103(a) rejections be withdrawn and the claims allowed.

Moreover, in determining whether one skilled in the art would have been motivated to select the claimed species from a genus, the M.P.E.P., at § 2144.08(II)(A)(1)(4), directs the Examiner to consider, among other things, the size of the genus, the express teachings of the prior art, and the predictability of the technology. The nine suggested members of the genus give rise to 511 possible species combinations. Furthermore, these combinations only encompass the members suggested at page 4, and do not encompass any additional members such as CD8 and TAC suggested at page 9.[4] Such a large number of combinations would preclude the testing of all combinations and would require any person to choose among them.[5] The only guidance in choosing a combination is provided by Scannon at page 9, which teaches that "typical combinations will include immunoglobulins recognizing CD4 and CD8; TAC and CD4; or CD7, CD11, and CD8." There is no suggestion that one should combine CD3 and CD7. CD3 is never even listed as being suitable for a typical combination. Therefore, Scannon does not expressly teach a combination of CD3 and

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[4] The addition of CD8 and TAC into the suggested members of the genus would raise the total number of combinations to 2047.

[5] Appellants were limited to the testing of only the eight possible combinations of three suggested molecules (*See*, Specification at page 8).

CD7 and provides no motivation for the selection of this particular combination from a large number of possibilities.

As discussed *supra*, biotechnology can be an unpredictable art. The mere recitation of using similar means to target diverse molecules is not indicative of a similar outcome. The list of possible target molecules that appear on T-cells represents a diverse group of cell surface molecules with numerous individual functions. How well the particular target molecules are expressed, as well as the diverse responses a particular cell may have to the binding of the targeting molecule to the target, both contribute to an unknown and variable efficacy for each target molecule selected. As such, it is unreasonable to infer that each possible target molecule has similar properties and will provoke a similar response when targeted by an immunotoxin. Therefore, the combination of CD3 and CD7 is not obvious as no reasonable expectation of success exists to the level found through the disclosed use of CD5.

Furthermore, Scannon actually directs the reader away from a combination of CD3 and CD7. At page 9, Scannon limits the scope of his disclosure by directing that: "[a]n immunosupressive immunotoxin composition will typically comprise immunoglobulins (complexed with toxins) that are capable of binding to and removing one or more T-cell subpopulations, preferably mature T-cells. Ideally, the immunoglobulins will only minimally, if at all, cross-react with other leukocyte subsets, particularly pluripotent stem cells." These statements teach away from the claimed invention as the claimed invention is specifically designed to react with another leukocyte subset, the NK-cells. The Specification, at pages 9 and 10, thoroughly describes the importance of NK-cell targeting because of the newly discovered role for NK-cells in the processes underlying GVHD.

As Scannon does not provide any motivation for the selection of a CD3/CD9 combination, and the Examiner fails to point to any other motivation, Appellants respectfully submit that rejections are reversed and claims 1, 15, 24, and 25 allowed. Further, as all other claims depend, either directly or indirectly from independent claims 1, 15, 24, and 25, Appellants respectfully request that the 35 U.S.C. § 103(a) rejection be completely withdrawn and all claims allowed.

Holding a Combination of CD3 and CD7 to be Obvious Would Amount to an Obvious to Try Standard

"Obvious to try" has consistently been held to not to be the standard for obviousness under 35 U.S.C. § 103. *See, e.g., In re Goodwin*, 576 F.2d 375, 377, 198 USPQ 1, 3 (CCPA 1978); *In re Tomlinson*, 363 F.2d 938, 150 USPQ 623 (CCPA 1966). The Federal Circuit has held that:

> The admonition that 'obvious to try' is not the standard under § 103 has been directed
> . . . [to cases where] what would have been 'obvious to try' would have been to vary all parameters or to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

In re O'Farrell, 853 F.2d at 903. This is precisely the case in regards to the claimed invention. For the nine possible target molecules listed on page 4 of Scannon, there are 511 possible combinations. When two additional target molecules are suggested at page 9, the number of combinations rises to 2047. One would have to try each of the numerous possible choices, all with varying degrees of success, until a combination that best suited the needs of the experimenter was arrived at. Where Scannon gives direction of which possible choices are likely to be successful, the combination of CD3 and CD7 is never mentioned (Scannon at page 9). CD3 is never suggested for use in any combination. Therefore, although it might have been "obvious to try" every possible combination of the target molecules suggested in Scannon, this would not render the claimed combination of CD3 and CD7 obvious under the meaning of 35 U.S.C. § 103.

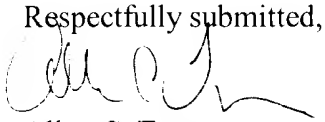
In re O'Farrell held that the claims therein were obvious because the prior art "contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful." *In re O'Farrell*, 853 F.2d at 902. In the present case, Scannon does suggest the claimed combination, thought not specifically and with over 500 other combinations in the same sentence. As detailed *supra* in the discussion of the 35 U.S.C. § 102(b) rejections, Scannon does not contain the required enabling methodology. Furthermore, the evidence suggesting that the targeting of CD3 and CD7 would be successful consists solely of testing antibodies directed against CD5, a wholly unrelated molecule that is targeted singly and not in combination. As such, the situation present *In re O'Farrell* is factually distinguishable from the present case, and for the reasons outlined therein and discussed above, the present claims are not made obvious by Scannon under 35 U.S.C. § 103(a),

For the foregoing reasons, Appellants respectfully submit that 35 U.S.C. § 103(a) rejection of claims 1, 15, 24, and 25 be withdrawn and the claims allowed. Further, as all other claims depend, either directly or indirectly from independent claims 1, 15, 24, and 25, Appellants respectfully request that the 35 U.S.C. § 103(a) rejection be completely withdrawn and all claims allowed.

(9) APPENDICES

A copy of claims 1-8, 10-13, 15, and 18-26 is appended hereto as "APPENDIX A."

Respectfully submitted,



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Enclosures: APPENDIX A - copy of claims 1-8, 10-13, 15, and 18-26

APPENDIX A

1. A pharmaceutical composition for eliminating or reducing the number of unwanted CD3 and/or CD7 positive cells, said pharmaceutical composition consisting essentially of: first molecules directed against CD3, and second molecules, distinct from said first molecules, said second molecules directed against CD7, wherein at least one of said first and said second molecules include a toxic moiety.

2. The method according to claim 15, wherein said second molecules specifically recognize CD7.

3. The pharmaceutical composition of claim 1, wherein said first molecules are antibodies.

4. The pharmaceutical composition of claim 1, wherein said second molecules are antibodies.

5. The pharmaceutical composition of claim 1, wherein said toxic moiety is ricin.

6. The pharmaceutical composition of claim 5, wherein said ricin is deglycosylated ricin A.

7. The pharmaceutical composition of claim 1, wherein said toxic moiety is chemically linked to said first and/or second molecules.

8. The pharmaceutical composition of claim 1, wherein said first and second molecules are provided with toxic moieties, which may be the same or different toxic moieties.

10. The pharmaceutical composition of claim 1, wherein said first molecules are gamma2B IgG.

11. The pharmaceutical composition of claim 5, wherein the toxic moiety is at least the equivalent dose of 25 micrograms of ricin A per square meter of body surface of a subject to which the composition is to be administered.

12. The pharmaceutical composition of claim 11, wherein the toxic moiety is at least the equivalent dose of 100 micrograms of ricin A per square meter of the subject=s body surface per administration.

13. The pharmaceutical composition of claim 11, wherein the toxic moiety is at most the equivalent dose of 25 mg of ricin A per square meter of the subject=s body surface per infusion.

15. A method of treating a disease state in a subject believed to be suffering therefrom, said disease state comprising at least one of Graft vs. Host disease, graft rejections, T-cell leukemias, T-cell lymphomas, other lymphomas, other CD3 and/or CD7 malignancies, autoimmune diseases, and infectious immune disease, said method comprising administering to the subject an amount of a pharmaceutical composition consisting essentially of: first molecules directed against a CD3

positive cell, and second molecules, distinct from said first molecules, directed against a CD7 positive cell, wherein at least the second molecules include a toxic moiety.

18. The pharmaceutical composition of claim 2, wherein said first molecules are antibodies.

19. The pharmaceutical composition of claim 18, wherein said second molecules are antibodies.

20. The pharmaceutical composition of claim 19, wherein said toxic moiety is deglycosylated ricin A.

21. The pharmaceutical composition of claim 19, wherein said toxic moiety is chemically linked to said first and second molecules.

22. The pharmaceutical composition of claim 21, wherein both said first and second molecules are provided with toxic moieties, which may be the same or different toxic moieties.

23. The pharmaceutical composition of claim 18, wherein said first molecules are gamma2B IgG.

24. A pharmaceutical composition for eliminating or reducing the number of unwanted CD3 and/or CD7 positive cells, said pharmaceutical composition consisting essentially of: anti-CD3 antibodies; and anti-CD7 antibodies, wherein each of said anti-CD3 antibodies and said anti-CD7 antibodies include a toxic moiety.

25. A method of treating a disease state in a subject believed to be suffering therefrom, said disease state comprising at least one of Graft vs. Host disease, graft rejections, T-cell leukemias, T-cell lymphomas, other lymphomas, other CD3 and/or CD7 malignancies, autoimmune diseases, and infectious immune diseases, said method comprising administering to the subject an amount of a pharmaceutical composition consisting essentially of: anti-CD3 antibodies; and anti-CD7 antibodies, wherein each of said anti-CD3 antibodies and said anti-CD7 antibodies include a toxic moiety.

26. The composition of claim 1, wherein said second molecules include a toxic moiety.